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Optimal Vasopressin Initiation in Septic Shock
The OVISS Reinforcement Learning Study

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IMPORTANCE Norepinephrine is the first-line vasopressor for patients with septic shock. When and whether a second agent, such as vasopressin, should be added is unknown.

OBJECTIVE To derive and validate a reinforcement learning model to determine the optimal initiation rule for vasopressin in adult, critically ill patients receiving norepinephrine for septic shock.

DESIGN, SETTING, AND PARTICIPANTS Reinforcement learning was used to generate the optimal rule for vasopressin initiation to improve short-term and hospital outcomes, using electronic health record data from 3608 patients who met the Sepsis-3 shock criteria at 5 California hospitals from 2012 to 2023. The rule was evaluated in 628 patients from the California dataset and 3 external datasets comprising 10 217 patients from 227 US hospitals, using weighted importance sampling and pooled logistic regression with inverse probability weighting.

EXPOSURES Clinical, laboratory, and treatment variables grouped hourly for 120 hours in the electronic health record.

MAIN OUTCOME AND MEASURE The primary outcome was in-hospital mortality.

RESULTS The derivation cohort (n = 3608) included 2075 men (57%) and had a median (IQR) age of 63 (56-70) years and Sequential Organ Failure Assessment (SOFA) score at shock onset of 5 (3-7 [range, 0-24, with higher scores associated with greater mortality]). The validation cohorts (n = 10 217) were 56% male (n = 5743) with a median (IQR) age of 67 (57-75) years and a SOFA score of 6 (4-9). In validation data, the model suggested vasopressin initiation in more patients (87% vs 31%), earlier relative to shock onset (median [IQR], 4 [1-8] vs 5 [1-14] hours), and at lower norepinephrine doses (median [IQR], 0.20 [0.08-0.45] vs 0.37 [0.17-0.69] µg/kg/min) compared with clinicians' actions. The rule was associated with a larger expected reward in validation data compared with clinician actions (weighted importance sampling difference, 31 [95% CI, 15-52]). The adjusted odds of hospital mortality were lower if vasopressin initiation was similar to the rule compared with different (odds ratio, 0.81 [95% CI, 0.73-0.91]), a finding consistent across external validation sets.

CONCLUSIONS AND RELEVANCE In adult patients with septic shock receiving norepinephrine, the use of vasopressin was variable. A reinforcement learning model developed and validated in several observational datasets recommended more frequent and earlier use of vasopressin than average care patterns and was associated with reduced mortality.

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JAMA. doi:10.1001/jama.2025.3046
Published online March 18, 2025.

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Sepsis is common and can be fatal, accounting for more than 270 000 deaths in the US annually.[1] Emergency care of patients with sepsis and life-threatening organ dysfunction includes fluid and vasopressor administration.[2]

International guidelines[3] recommend using norepinephrine as the first-line vasopressor. They suggest considering vasopressin as a second-line agent when blood pressure remains poorly responsive to norepinephrine. However, septic shock is a dynamic condition, complicating the decision to initiate vasopressin. Although vasopressin use has increased,[4] it is used inconsistently, and there is little guidance from randomized clinical trials on optimal timing.

Reinforcement learning is a branch of machine learning where a virtual agent learns from trial and error an optimized set of treatment rules to maximize the probability of a good outcome.[5] It is well-suited for complex, dynamic problems like septic shock. The Optimal Vasopressin Initiation in Septic Shock (OVISS) study applied reinforcement learning in multiple electronic health record datasets to derive, validate, and measure the treatment implications of a vasopressin initiation rule optimized to improve both short-term and hospital outcomes among adult critically ill patients receiving norepinephrine for septic shock.

Key Points

Question Does a reinforcement learning model identify the optimal initiation rule for vasopressin in patients with septic shock who are receiving norepinephrine?

Findings Among 14 453 critically ill patients with septic shock from 232 hospitals in 4 independent datasets, a reinforcement learning model recommended the initiation of vasopressin more frequently, sooner, at a lower norepinephrine dose, and at a lower organ failure score compared with the average observed actions of clinicians. Patients in whom vasopressin was initiated similarly, vs differently, to that recommended by the reinforcement learning model had statistically significantly reduced in-hospital mortality (adjusted odds ratio, 0.81).

Meaning The initiation of vasopressin following recommendations by a reinforcement learning model was associated with decreased mortality in patients with septic shock already receiving norepinephrine.

Methods

This study is reported according to the TRIPOD+AI guidelines[6] (Supplement 1). Certified deidentification removed the institutional review board approval requirement for the University of California, San Francisco (UCSF) data. Medical Information Mart for Intensive Care (MIMIC-IV) and eICU Collaborative Research Database (eICU-CRD) data are publicly available. Data from University of Pittsburgh Medical Center (UPMC) were transferred to UCSF under a data-sharing agreement (DUA00003086). The University of Pittsburgh Institutional Review Board waived the requirement of written informed consent (IRB number: STUDY19030218).

Derivation and Validation Cohorts

We developed a reinforcement learning model to identify the optimal vasopressin initiation strategy (referred to as the *reinforcement learning rule*) in critically ill patients with septic shock who are receiving norepinephrine. We assessed the treatment implications of the rule by comparing the recommendations provided by the reinforcement learning rule with clinicians' actual vasopressin initiation practices (referred to as the *clinician-observed action*).

First, the training, testing, and internal validation of the model used data from the UCSF De-Identified Clinical Data Warehouse.[7] These data included more than 120 000 critically ill admissions from 2012 to 2023. We included unique patients experiencing their first episode of community- or hospital-onset septic shock, defined by the Sepsis-3 criteria,[2] which could be met in either the emergency department or intensive care unit (ICU), and were already receiving norepinephrine.

Second, to externally validate the reinforcement learning model, we used 3 datasets: MIMIC-IV,[8] eICU-CRD,[9] and a previously curated electronic health record dataset of adult critically ill patients admitted to 18 hospitals at UPMC from 2018 to 2020.[10] These 3 databases include more than 250 000 admissions in 227 US hospitals from 2008 to 2020. MIMIC-IV and eICU-CRD contain only data during intensive care, while UPMC includes data irrespective of critical care location. Abstracted data included demographics, vital signs, severity of illness, treatment, and laboratory results. Race was derived using fixed categories consistent with the Centers for Medicare & Medicaid Services meaningful use dataset. Race and ethnicity data were collected to ensure fairness and equity.

Data Preparation for Reinforcement Learning Models

UCSF data were split into derivation (training and test) and internal validation sets using a 70/15/15 random splitting procedure. The validation cohorts consisted of the UCSF internal validation set and 3 external datasets (**Figure 1**). To prepare for model training,[11,12] each hospital stay was considered as a single trajectory, discretized into 1-hour epochs starting at t = 1 hour after shock onset. Data were truncated at the earliest of shock recovery (defined as ≥12 hours off norepinephrine), ICU discharge (dead or alive), or t = 120 hours.

Each patient was described by a fixed set of baseline characteristics, including age, sex, height, weight, race and ethnicity, Sequential Organ Failure Assessment (SOFA) score (range, 0-24 points, with higher scores indicating worse organ function), mean arterial pressure, serum lactate, norepinephrine dose, fluid before inclusion, mechanical ventilation, continuous kidney replacement therapy, and Charlson Comorbidity Index score, a method of categorizing comorbidities based on *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis scores in administrative data (range, 0-37). Other data, such as source of infection, microbiology, or time to source control, were not captured or would not be pragmatically available to clinicians at the time of vasopressor initiation.

Each 1-hour epoch was described by 14 clinical, time-varying features (eTable 1 in Supplement 1), including patient vital signs, laboratory measurements, and organ support (eg, mechanical ventilation, kidney replacement therapy).

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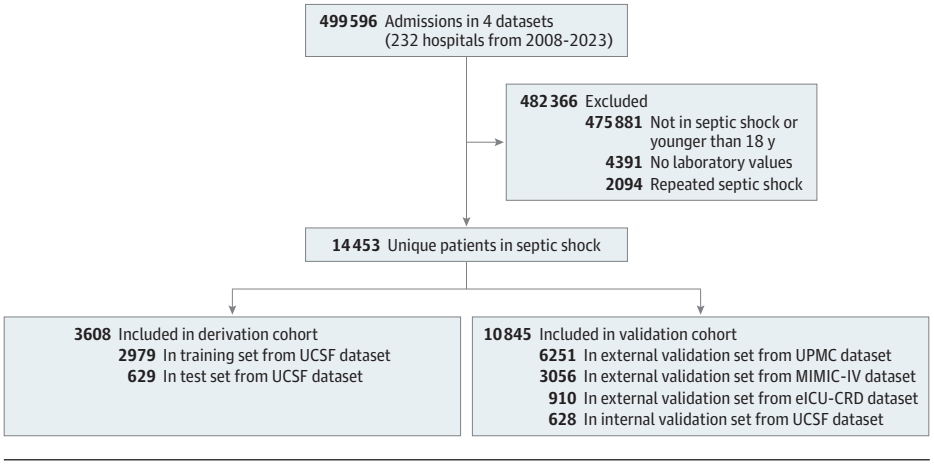
Figure 1. Patient Accrual in a Study of a Reinforcement Learning Rule for Vasopressin Initiation in Septic Shock


499 596 Admissions in 4 datasets
(232 hospitals from 2008-2023)
482 366 Excluded
475 881 Not in septic shock or younger than 18 y
4391 No laboratory values
2094 Repeated septic shock
14 453 Unique patients in septic shock
3608 Included in derivation cohort
2979 In training set from UCSF dataset
629 In test set from UCSF dataset
10 845 Included in validation cohort
6251 In external validation set from UPMC dataset
3056 In external validation set from MIMIC-IV dataset
910 In external validation set from eICU-CRD dataset
628 In internal validation set from UCSF dataset

eICU-CRD indicates eICU Collaborative Research Database; MIMIC-IV, Medical Information Mart for Intensive Care; UCSF, University of California, San Francisco; UPMC, University of Pittsburgh Medical Center.

Additional data included the volume of intravenous fluids administered up to the current epoch after shock onset, including colloids but excluding transfusion and medication fluids. The mean vasopressor doses administered to each patient were abstracted in each epoch. If a measurement was unavailable for a given variable in a specific epoch, the last observed value was carried forward, reflecting clinical practice.[13] If multiple measurements were available for a variable during an epoch, the mean value was used.

Model Training

A reinforcement learning model is a specific type of machine learning algorithm where an agent learns how to make decisions by interacting with an environment. The agent aims to maximize rewards over time by choosing actions based on the current state, with the decision-making process guided by the likelihood of future outcomes (eMethods and eFigure 1 in Supplement 1).

We defined the action for each epoch as a binary decision (eg, "start vasopressin" or "do not start vasopressin"). The model reward per epoch was calculated as a weighted combination of in-hospital mortality, changes in serum lactate levels, mean arterial pressure, SOFA score,[14] and norepinephrine dose, with each element scaled by a predetermined coefficient (eMethods in Supplement 1). Epsilon, a parameter that balances exploration vs exploitation, was set at 0.99. We further adjusted the model hyperparameters (ie, parameters that influence how the learning process happens) and determined the optimal number of reinforcement learning algorithm iterations (eMethods in Supplement 1). Assumptions regarding model parameters were tested in sensitivity analyses (eMethods in Supplement 1).

Statistical Analysis

Continuous variables were described as mean (SD) or median (IQR) and categorical variables as counts (percentage). For descriptive analyses, the significance level was set at .05, with no adjustment for multiple comparisons.

Evaluation and Treatment Implications of the Reinforcement Learning Rule

Model performance was evaluated using weighted importance sampling,[15] an off-policy evaluation[16] method that compares the mean individual reward obtained with the reinforcement learning rule with the mean reward obtained from the clinician-observed action. Weighted importance sampling and the weighted importance sampling difference between the reinforcement learning rule and the clinician-observed action were calculated in both internal and external validation data for the overall reward and individual reward components (eMethods in Supplement 1).[17-19]

We evaluated the treatment implications of the rule recommended by the reinforcement learning algorithm in the 3 external datasets. We described the percentage of patients who would receive vasopressin, timing of initiation relative to shock onset, dose of norepinephrine, SOFA score, and serum lactate at vasopressin initiation under the clinician-observed action and under the optimal reinforcement learning rule.

We used weighted pooled logistic regression to estimate the adjusted odds of in-hospital mortality, comparing patients in whom care was similar vs different to the reinforcement learning rule in each time block, treating time as a discrete variable. Specifically, we defined concordance in each time block as present if the clinician-observed action matched the action recommended by the reinforcement learning algorithm. To account for time-varying confounders and treatment decisions being made hourly, the regression model was also weighted using inverse probability of treatment weighting[20] (eMethods in Supplement 1). Predicted probabilities from the model were used to estimate survival curves, censored at 120 hours for illustration. This evaluation also included assessment of risk-adjusted odds of in-hospital mortality, comparing several simple rules for vasopressin initiation vs observed clinical actions, including (1) vasopressin initiation at a serum lactate level greater than 4 mmol/L, (2) norepinephrine dose greater than 0.7 µg/kg/min, and (3) mean arterial pressure less than 65 mm Hg and more than

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Table 1. Patient Characteristics[a]

Characteristic	Derivation cohort, No. (%)[b]	Internal and external validation cohorts (validation set), No. (%)[b]			
	UCSF training and test sets (n = 3608)	UCSF internal (n = 628)	MIMIC-IV (n = 3056)	eICU-CRD (n = 910)	UPMC (n = 6251)
Summary of datasets					
Enrollment period	2012-2023	2012-2023	2008-2019	2014-2015	2019-2020
No. of hospitals	5	5	1	208	18
Total No. of admissions	119 730	119 730	76 540	200 859	102 467
Setting	Integrated health system			Health systems across US	Integrated health system in Pennsylvania
	California	California	Boston		
Patient characteristics					
Age, median (IQR), y	63 (56-70)	63 (56-69)	67 (56-77)	67 (57-77)	66 (57-75)
Admission weight, median (IQR), kg	74 (62-90)	74 (61-90)	80 (66-96)	75 (64-96)	77 (54-97)
Sex					
Male	2075 (57)	351 (56)	1820 (59)	468 (51)	3455 (55)
Female	1533 (43)	277 (44)	1236 (41)	442 (49)	2796 (45)
Race[c]					
Black	342 (10)	65 (11)	262 (9)	86 (9)	716 (11)
White	1654 (45)	270 (44)	1858 (61)	640 (70)	4970 (80)
Other/unknown[d]	1612 (45)	293 (45)	936 (31)	184 (21)	565 (9)
Charlson Comorbidity Index score, mean (SD)[e]	4 (2)	4 (1)	5 (2)	5 (3)	2 (1)
Clinical presentation					
Heart rate, mean (SD), beats/min	97 (25)	99 (24)	90 (22)	98 (24)	95 (25)
Systolic blood pressure, median (IQR), mm Hg	105 (81-121)	112 (88-119)	102 (88-117)	104 (85-113)	102 (91-116)
Respiration rate, mean (SD), breath/min	21 (6)	20 (5)	20 (6)	22 (8)	22 (7)
Temperature, mean (SD), °C	37.1 (1.9)	37.0 (1.9)	36.7 (1.0)	36.7 (1.3)	36.6 (1.4)
Glasgow Coma Scale score, mean (SD)	11 (4)	10 (5)	10 (5)	12 (4)	10 (5)
SOFA score, median (IQR)[f]	5 (3-7)	5 (3-9)	4 (3-6)	4 (3-7)	5 (3-8)
Biological results					
White blood cell count, median (IQR), x10^9/L	13.2 (9.1-17.8)	13.2 (9.1-18.0)	12.5 (8.2-18.3)	12.4 (8.0-18.3)	13.8 (8.6-20.2)
Serum lactate, median (IQR), mmol/L	1.9 (1.2-3.5)	1.8 (1.2-3.8)	1.8 (1.7-3.0)	1.8 (1.6-3.4)	2.8 (1.6-5.1)
Serum creatinine, median (IQR), mg/dL	1.3 (0.9-2.2)	1.3 (0.8-2.2)	1.4 (1.0-2.1)	1.7 (1.1-2.7)	1.7 (1.1-2.8)
Blood urea nitrogen, median (IQR), mg/dL	27 (17-45)	25 (15-44)	27 (17-42)	35 (23-51)	33 (20-51)
Hemoglobin, mean (SD), g/dL	10.3 (2.3)	10.4 (2.3)	10.6 (2.7)	10.1 (2.6)	10.3 (2.8)
Platelet count, median (IQR), x10^9/L	194 (131-289)	192 (130-287)	190 (129-270)	168 (97-237)	171 (103-250)
International normalized ratio, median (IQR)	1.6 (1.2-2.0)	1.5 (1.2-1.9)	1.3 (1.2-1.7)	1.4 (1.2-1.8)	1.6 (1.3-2.1)
Bilirubin, median (IQR), mg/dL	0.9 (0.4-1.1)	0.9 (0.5-1.1)	0.7 (0.4-1.3)	0.7 (0.4-1.2)	1.1 (0.6-2.3)
Organ support					
Norepinephrine dose, median (IQR), µg/kg/min	0.05 (0.03-0.10)	0.06 (0.03-0.10)	0.12 (0.06-0.23)	0.26 (0.12-0.46)	0.16 (0.06-0.45)
Vasopressin introduction during shock	908 (25)	151 (24)	1485 (48)	179 (20)	1522 (24)
Mechanical ventilation[g]					
At shock onset	692 (19)	127 (20)	22 (1)	77 (8)	3551 (57)
During the entire trajectory	1252 (35)	225 (35)	225 (9)	124 (14)	4673 (75)

(continued)

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Table 1. Patient Characteristics[a] (continued)

Characteristic	Derivation cohort, No. (%)[b]	Internal and external validation cohorts (validation set), No. (%)[b]			
	UCSF training and test sets (n = 3608)	UCSF internal (n = 628)	MIMIC-IV (n = 3056)	eICU-CRD (n = 910)	UPMC (n = 6251)
Kidney replacement therapy[h]					
At shock onset	168 (5)	27 (4)	22 (1)	11 (1)	421 (7)
During the entire trajectory	268 (7)	36 (6)	504 (16)	141 (15)	1278 (20)
Outcome					
In-hospital mortality	1603 (44)	254 (41)	1186 (38)	256 (28)	2705 (43)

Abbreviations: EHR, electronic health record; eICU-CRD, eICU Collaborative Research Database; MIMIC-IV, Medical Information Mart for Intensive Care; SOFA, Sequential Organ Failure Assessment; UCSF, University of California, San Francisco; UPMC, University of Pittsburgh Medical Center.

SI conversion factors: To convert white blood cell count to /μL, divide by 0.001; lactate to mg/dL, divide by 0.111; creatinine to μmol/L, multiply by 88.4; urea nitrogen to mmol/L, multiply by 0.357; hemoglobin to g/L, multiply by 10.0; platelet count to $\times 10^3$/μL, divide by 1.0; bilirubin to μmol/L, multiply by 17.104.

[a] Each value represents the first-hour measurement at shock onset when available; otherwise, the most recent value from the previous 24 hours was used.

[b] Unless otherwise indicated.

[c] Race was self-reported by patients and recorded in the EHR. It was categorized using fixed classifications aligned with the Centers for Medicare & Medicaid Services' EHR meaningful use dataset.

[d] Includes Asian, Chinese, Filipino, Hawaiian, Hispanic, Native American/American Indian, and Other Pacific Islander.

[e] A method of categorizing comorbidities of patients based on the *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis scores found in administrative data; score ranges from 0 to 37.

[f] Corresponds to the severity of organ dysfunction, reflecting 6 organ systems each; scores range from 0 to 4 points for the cardiovascular, hepatic, hematologic, respiratory, neurological, and renal systems. The total score range is 0 to 24 points.

[g] Corresponds to endotracheal or tracheostomy tube to assist or replace spontaneous breathing.

[h] Term includes intermittent hemodialysis and continuous kidney replacement therapy to assist kidney function.

12 hours from shock onset. Secondary outcomes included the use of mechanical ventilation and kidney replacement therapy during the patient trajectory, conditional on not yet receiving that level of organ support.

Robustness of Results to Confounding

Both the derivation of the rule and all validation exercises were conducted in observational data. As such, the study is susceptible to confounding bias, where features about the patients not captured in the data nevertheless influenced both clinician actions and patient outcomes. Thus, we conducted 3 evaluations of the robustness of our results to confounding (eMethods in Supplement 1): (1) calculation of E-values,[21] (2) inclusion of ICU- and hospital-level features, and (3) falsification analyses, using a negative outcome ("death occurring on odd vs even time blocks") and a negative exposure ("introduce vasopressin systematically 2 hours after shock onset").[22]

Sensitivity Analyses

Several sensitivity analyses were performed. First, we attempted further confounder control by repeating analyses in restricted cohorts,[23,24] including (1) patients for whom the model recommended vasopressin and who actually received it, (2) patients for whom the model advised against introducing vasopressin at any point in their treatment trajectory, (3) after excluding patients with severe acute kidney injury (eMethods in Supplement 1), and (4) patients in whom vasopressin was started within 48 hours. These smaller cohorts remove patients in whom clinicians may have important unmeasured biases about the initiation of vasopressin. Second, we assessed models after varying epsilon from 0.99 to 0.95 and 0.90. Third, we repeated models using 2-hour time epochs. Fourth, we used alternative weighting for the reward in which each component of the reward function was given the same weight and repeated the analyses.

Reinforcement Learning Model Interpretability

To enhance interpretability, the contribution of each feature in the reinforcement learning rule was quantified using Shapley Additive Explanations (SHAP) values.[25] Specifically, we analyzed SHAP values to determine the relative importance of clinical features at the time the model recommended vasopressin initiation (eMethods in Supplement 1).

Model Fairness and Equity

To study model fairness and equity, we stratified the evaluation analyses and treatment implications by sex (male, female), race (Black, White, and other/unknown), and age (<65 and ≥65 years).

Results

Patients

There were 14 453 adult patients with septic shock receiving norepinephrine in the 4 datasets (Figure 1; **Table 1**). Of these, 3608 were randomly selected from the UCSF cohort for the derivation cohort (median [IQR] age, 63 [56-70] years; 2075 [57%] were male; median SOFA score at shock onset, 5 [3-7]). An additional 628 UCSF patients comprised the internal validation cohort, and external cohorts included 3056 patients from MIMIC-IV, 910 patients from eICU-CRD, and 6251 patients from UPMC (overall median [IQR] age, 67 [57-76] years; 5743 [56%] were male; median SOFA score at shock onset, 6 [4-9]).

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Table 2. Patient Data in the Epoch Containing Vasopressin Initiation in External Validation Sets

	Overall			MIMIC-IV			eICU-CRD			UPMC		
	Clinician-observed action	Reinforcement learning rule	*P* value	Clinician-observed action	Reinforcement learning rule	*P* value	Clinician-observed action	Reinforcement learning rule	*P* value	Clinician-observed action	Reinforcement learning rule	*P* value
Patients with vasopressin started, No. (%)	3186 (31)	8884 (87)	<.001	1485 (47)	2649 (87)	<.001	179 (20)	813 (89)	<.001	1522 (24)	5422 (87)	<.001
Norepinephrine dose, median (IQR), μg/kg/min	0.37 (0.17-0.69)	0.2 (0.08-0.45)	<.001	0.28 (0.14-0.40)	0.16 (0.08-0.30)	<.001	0.68 (0.35-1.35)	0.35 (0.13-1.12)	<.001	0.6 (0.20-1.40)	0.2 (0.08-0.51)	<.001
Time since shock onset, median (IQR), h	5 (1-14)	4 (1-8)	<.001	4 (1-12)	5 (2-9)	.01	6 (2-14)	3 (1-7)	<.001	6 (2-17)	4 (1-7)	<.001
SOFA score, median (IQR)[a]	9 (6-12)	7 (5-10)	<.001	10 (8-12)	10 (7-12)	<.001	13 (11-15)	11 (9-13)	<.001	7 (5-10)	6 (3-8)	<.001
Serum lactate, median (IQR), mmol/L	3.6 (1.8-6.8)	2.5 (1.7-4.9)	<.001	2.6 (1.7-5.2)	2.3 (1.7-4.5)	<.001	3.2 (1.7-5.9)	1.7 (1.1-2.9)	<.001	4.7 (2.5-8.8)	2.7 (1.7-5.3)	<.001

Abbreviations: eICU-CRD, eICU Collaborative Research Database; MIMIC-IV, Medical Information Mart for Intensive Care; SOFA, Sequential Organ Failure Assessment; UPMC, University of Pittsburgh Medical Center.

SI conversion factor: To convert lactate to mg/dL, divide by 0.111.

[a] Corresponds to the severity of organ dysfunction, reflecting 6 organ systems each; scores range from 0 to 4 points for the cardiovascular, hepatic, hematologic, respiratory, neurological, and renal systems. The total score range is 0 to 24 points.

In the 3 external datasets, clinicians initiated vasopressin in 3186 of 10 217 patients already receiving norepinephrine (31%) (**Table 2**). Vasopressin was started at a median (IQR) SOFA score of 9 (6-12), a median 5 (1-14) hours after shock onset, norepinephrine dose of 0.37 (0.17-0.69) μg/kg/min, and serum lactate of 3.6 (1.8-6.8) mmol/L. In-hospital mortality ranged from 28% to 43%. UPMC patients received more organ support and the initiation of vasopressin by clinicians began at a higher norepinephrine dose (UPMC, 0.6 μg/kg/min vs UCSF, 0.14 μg/kg/min).

Evaluation of Reinforcement Learning Model for Vasopressin Initiation

Among 2362 patients in whom vasopressin was recommended by the reinforcement learning rule and initiated by clinicians during their trajectory, 338 (14%) had vasopressin initiated in the same epoch as the reinforcement learning rule recommendation. Compared with the clinician-observed action in external data, the reinforcement learning model suggested vasopressin initiation in more patients (8884 of 10 217 [87%]; $P < .001$), at a lower median (IQR) SOFA score (7 [5-10]; $P < .001$), earlier after shock onset (4 [1-8] hours; $P < .001$), at lower norepinephrine doses (0.20 [0.08-0.45] μg/kg/min; $P < .001$), and at lower serum lactate (2.5 [1.7-4.9] mmol/L; $P < .001$) (**Figure 2**). These results were consistent across each of the 3 validation sets, except for timing of vasopressin initiation in MIMIC-IV (median [IQR], 4 [1-12] hours for clinician-observed action vs 5 [2-9] hours for reinforcement learning rule; $P = .01$) (Table 2; eTable 2 in Supplement 1).

The reinforcement learning rule outperformed the clinician-observed action (weighted importance sampling difference, 31 [95% CI, 15-52]) (**Figure 3**). The weighted importance sampling difference was consistent for each component of the reward (in-hospital mortality, 29 [95% CI, 27-34]; mean arterial pressure, 32 [95% CI, 29-36]; SOFA score, 28 [95% CI, 21-37]; norepinephrine dose, 35 [95% CI, 26-49]; and serum lactate, 25 [95% CI, 22-27]). These findings were consistent across each of the datasets (Figure 3; eTable 3 in Supplement 1).

Using pooled logistic regression with inverse probability of treatment weighting in 3 external datasets, concordance with the reinforcement learning rule in each time block was associated with decreased odds of in-hospital mortality at each time point (adjusted odds ratio [aOR], 0.81 [robust 95% CI, 0.73-0.91]) (**Figure 4**; eFigure 2 in Supplement 1). Reinforcement learning rule concordance was also associated with reduced odds of requiring kidney replacement therapy at each time point (aOR, 0.47 [robust 95% CI, 0.46-0.49]), but not with the odds of requiring mechanical ventilation at each time point (aOR, 1.00 [robust 95% CI, 0.96-1.04]) (eTable 4 in Supplement 1). More simple decision rules for initiating vasopressin were associated with statistically significantly worse odds of in-hospital mortality compared with the clinician-observed action (Figure 4).

Robustness to Confounding

First, these analyses were supported by an E-value of 1.46. Second, when adding ICU- and hospital-level variables to

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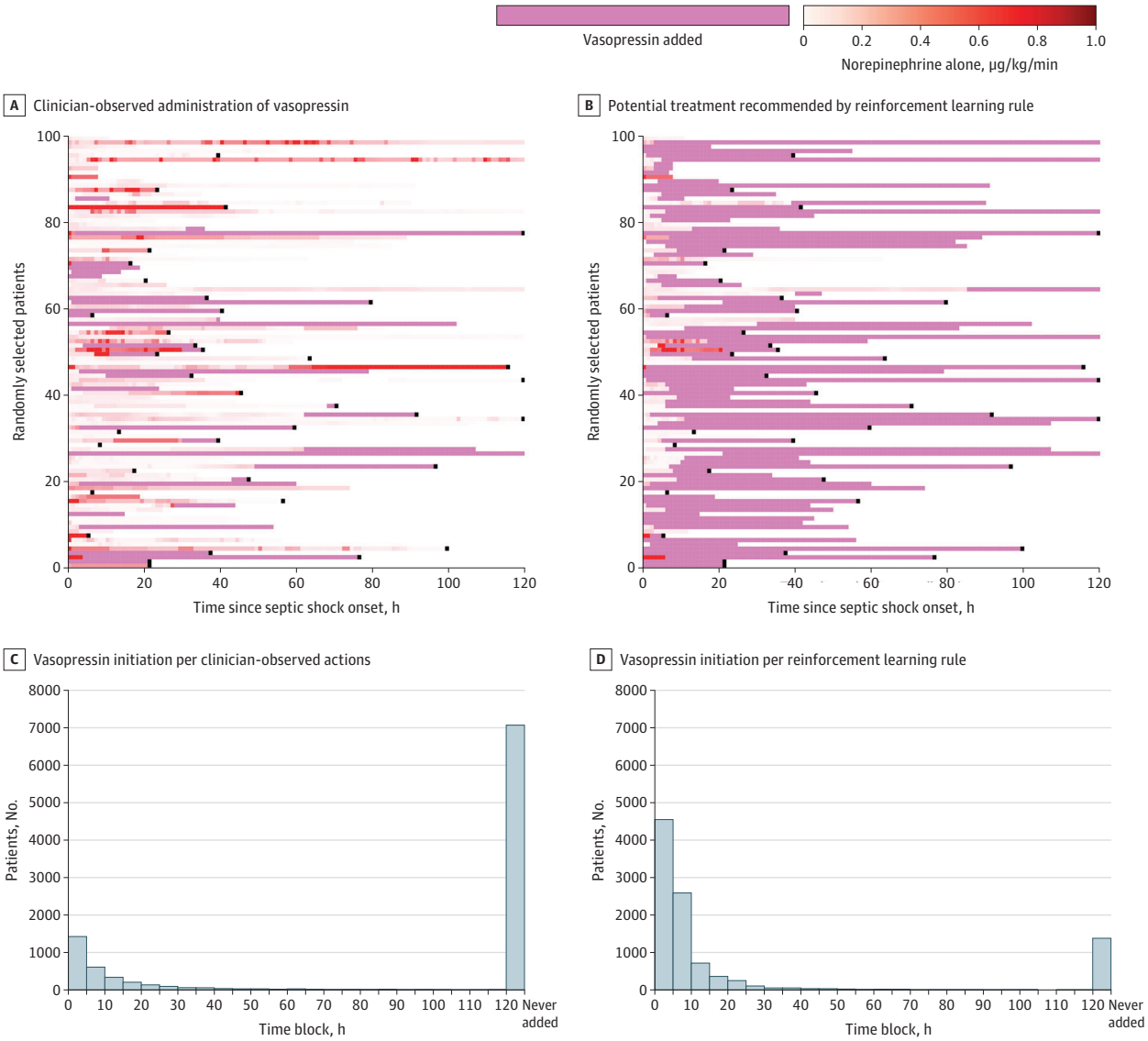
Figure 2. Comparison of Clinician-Observed Administration of Vasopressin With Treatment Recommended by the Reinforcement Learning Rule


Vasopressin added
0 0.2 0.4 0.6 0.8 1.0
Norepinephrine alone, µg/kg/min
A Clinician-observed administration of vasopressin
B Potential treatment recommended by reinforcement learning rule
Randomly selected patients
Time since septic shock onset, h
C Vasopressin initiation per clinician-observed actions
D Vasopressin initiation per reinforcement learning rule
Patients, No.
Time block, h
Never added

A and B, 100 randomly selected patients included in each panel. Each line represents 1 patient trajectory. Red indicates the patient received norepinephrine alone, with a color scale representing the norepinephrine dose, and purple indicates both norepinephrine and vasopressin were infused. White corresponds to discharge alive. Black boxes at the end of the trajectory represent mortality. C, Number of patients in whom vasopressin was initiated in each time block for the clinical observed actions. D, Number of patients in whom vasopressin was initiated per the reinforcement learning rule.

models, the association between concordance and the odds of in-hospital mortality at each time point was consistent (UPMC aOR for in-hospital mortality, 0.87 [95% CI, 0.75-1.01]) (eTable 5 in Supplement 1). Third, falsification analyses found no association between concordance with the reinforcement learning rule and the negative outcome (aOR, 1.17 [robust 95% CI, 0.94-1.44]) nor between the negative exposure and mortality (aOR, 1.10 [robust 95% CI, 0.94-1.30]).

Sensitivity Analyses

The model performed similarly among restricted cohorts of patients in whom vasopressin was recommended or recommended early (within 48 hours). The findings were neutral when no vasopressin was recommended by the rule or if vasopressin was already initiated by clinicians early (within 12 hours) (eTable 5 in Supplement 1). When the epsilon parameter was varied, the weighted importance sampling results were similar, but the association with mortality was muted (epsilon, 0.95; aOR for in-hospital mortality, 0.91 [95% CI, 0.79-1.11]). Models were not statistically significant using a 2-hour time epoch or alternative reward weighting (eTable 5 in Supplement 1).

Model Interpretability

According to SHAP values, the 4 most important features informing the vasopressin initiation reinforcement learning rule

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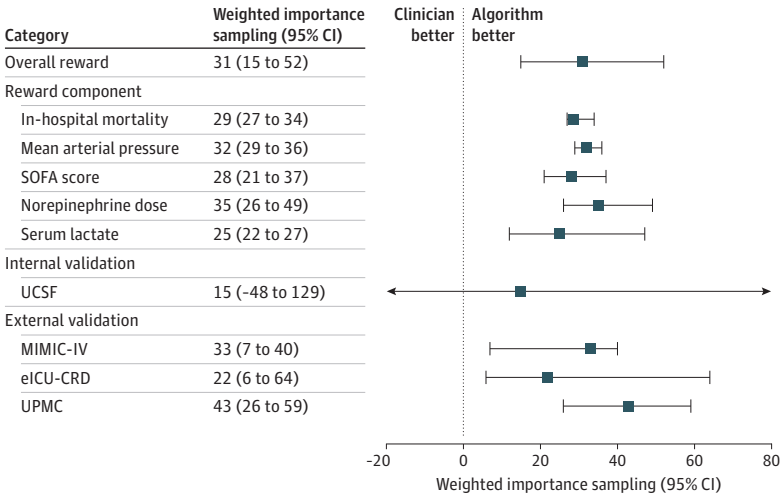
Figure 3. Weighted Importance Sampling



Weighted importance sampling measures the mean individual reward obtained using the reinforcement learning rule and the mean reward associated with the clinician-observed actions. Weighted importance sampling was estimated in the internal and external validation sets (overall reward) for each reward component independently (reward component) and each internal and external validation set separately (internal/external validation). Results are presented as the difference in weighted importance sampling between the reinforcement learning rule and the clinician's observed rule, with bootstrapped 95% CIs. A negative weighted importance sampling difference indicated that the clinician-observed actions were associated with a higher reward, whereas a positive difference suggested the reinforcement learning rule yielded a higher reward. For example, the reinforcement learning rule was associated with a higher overall reward (weighted importance sampling difference, 31 [95% CI, 15-52]) as well as higher rewards for each component individually. In the UCSF internal validation set, the lower bound of the 95% CI crossed 0 (weighted importance sampling difference, 15 [95% CI, −48 to 129]), indicating that the overall reward obtained with the reinforcement learning rule was not statistically higher than that associated with the clinician-observed actions. The dotted line is the reference line (ie, no difference in weighted importance sampling between the algorithm rule and the clinician-observed actions).

eICU-CRD indicates eICU Collaborative Research Database; MIMIC-IV, Medical Information Mart for Intensive Care; SOFA, Sequential Organ Failure Assessment; UCSF, University of California, San Francisco; UPMC, University of Pittsburgh Medical Center.

were the time since shock onset, SOFA score, norepinephrine dose, and serum lactate at the time of vasopressin initiation (eFigure 3 in Supplement 1).

Fairness and Equity

The reinforcement learning rule showed no significant differences in recommendations for vasopressin initiation across the sex, race, and age subgroups (eFigure 4 in Supplement 1). There was also no significant difference in the evaluation or treatment implications of the reinforcement learning rule between the sex, race, and age subgroups (eTables 7 and 8 in Supplement 1).

Discussion

In a multicenter study of 232 hospitals and 14 453 patients in 4 datasets, this study derived, validated, and tested the clinical implications of a reinforcement learning model for vasopressin initiation in patients with septic shock already receiving norepinephrine. Compared with average clinician actions, the reinforcement learning rule was associated with a higher reward and reduced in-hospital mortality.

International practice guidelines suggest vasopressin as the second-line vasopressor if the mean arterial pressure remains inadequate despite low to moderate norepinephrine doses.[3] While vasopressin use has increased,[4] there are many unanswered questions. There are no randomized clinical trials that identify the optimal administration strategy, at what dose of norepinephrine to initiate vasopressin, or how to wean the drug. Randomized clinical trials, even those with 3 to 4 groups, may not capture the universe of possible treatment approaches for vasopressor use. Meanwhile, prior work uses reinforcement learning to optimize complex medical decisions, such as for the treatment of diabetes[26,27] or mechanical ventilation.[18] Thus, this study reports the first evaluation of reinforcement learning to enhance clinical decision-making for the initiation of vasopressin in septic shock. The OVISS reinforcement learning rule suggests initiating vasopressin at a lower norepinephrine dose compared with the average use of nuanced clinicians in practice. These findings align with subgroup analyses from the Vasopressin and Septic Shock Trial (VASST),[28] which suggested that patients who received vasopressin may have improved outcomes in a less severe shock stratum (interaction $P = .10$).

The reinforcement learning rule for vasopressin initiation may improve outcomes through several mechanisms. First, although clinicians had access to the same data, the rule may capture subclinical features about the mechanisms and benefits of vasopressin and thus assign different emphases to clinical data to drive vasopressin initiation than assessments by clinicians. Second, from a biological perspective, exogenous vasopressin may compensate for the relative deficiency observed in septic shock.[29-32] Third, vasopressin may

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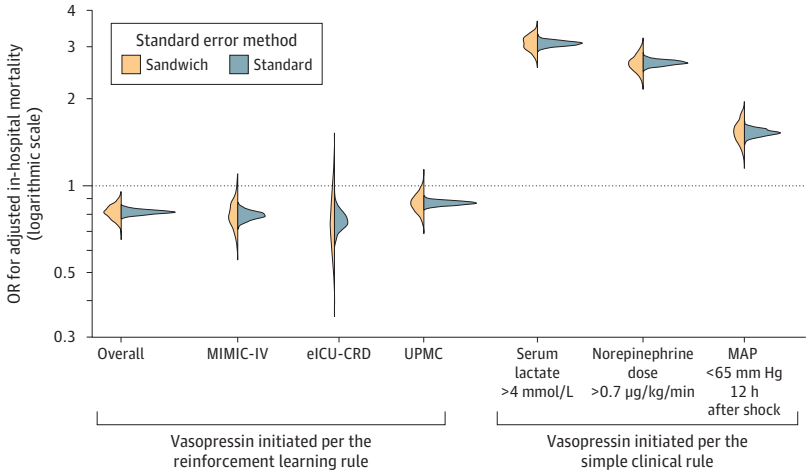
Figure 4. Risk-Adjusted Odds of In-Hospital Mortality Comparing Concordance With the Reinforcement Learning Rule or a Simple Clinical Rule With Clinician-Observed Actions



Distribution using a regular standard error estimator or a robust standard error estimator. Reinforcement learning rule results displayed for combined validation cohort as well as each individual cohort. Simple clinical decision rule results displayed for combined validation cohort only. The risk-adjusted odds for in-hospital mortality were derived from inverse probability of treatment weighted pooled logistic regression models, adjusting for baseline and time-varying confounders. The results for vasopressin initiated per the reinforcement learning rule show the ORs for in-hospital mortality of concordance with the reinforcement learning rule in each 1-hour epoch compared with the clinician-observed actions for the overall external validation set and for each external validation dataset separately. The results for vasopressin initiated per the simple clinical rule show the ORs for in-hospital mortality of concordance with 3 independent simple clinical rules for vasopressin initiation in each 1-hour epoch for the overall external validation set. The 3 simple rules are: "initiate vasopressin when serum lactate is >4 mmol/L," "initiate vasopressin when norepinephrine dose is >0.7 µg/kg/min," and "initiate vasopressin when MAP is <65 mm Hg and time from shock onset is at least 12 hours."

eICU-CRD indicates eICU Collaborative Research Database; MAP, mean arterial pressure; MIMIC-IV, Medical Information Mart for Intensive Care; OR, odds ratio; UPMC, University of Pittsburgh Medical Center.

increase glomerular filtration pressure,[33] consistent with the results herein where rule concordance was associated with a lower need for kidney replacement therapy. Fourth, prior studies like Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH) and VASST demonstrate vasopressin's catecholamine-sparing effects, which may reduce the adrenergic burden and the need for high norepinephrine doses, perhaps lowering the risk of tachyarrhythmias or myocardial ischemia. Fifth, earlier vasopressin administration may reflect increased clinical vigilance and aggressive monitoring, potentially leading to improved outcomes. Alternatively, although the reinforcement learning rule appears to be associated with improved outcomes, there is the possibility that confounding obscured the true effects.

Limitations

This study has limitations. First, the study did not prospectively test the reinforcement learning rule, instead using offline data. Future bedside use requires more rigorous assessments using randomized clinical trials. Second, the model may have limited transportability to underrepresented groups in the derivation data.[34] To mitigate this, 4 datasets from more than 200 hospitals were used. The study also tested the reinforcement learning rule in age, sex, and race strata, finding no significant differences. These analyses did not include low- or middle-income countries with varying practice.[35] Third, because the models were derived offline and evaluated using existing data, there were several factors, such as clinician subjectivity, which were not fully captured by the model. Analyses after adjustment for hospital- or ICU-level characteristics were consistent. Fourth, models do not include unmeasured variables, such as infectious source or timing of source control, or seek to vary the lag adjustment for confounding control. For the observed relationships to be fully explained by these and other unmeasured confounders, that confounder would need to increase both the likelihood of adhering to the reinforcement learning rule and mortality by more than 45%. Fifth, the study addressed missing values by carrying forward the last observed value, a common method that simplifies analysis and avoids introducing noise. It offers a conservative estimate and was used in prior studies with reinforcement learning.[11,36] Sixth, the reinforcement learning rule recommended the initiation of vasopressin, not a dosing strategy or protocol for weaning. Seventh, long-term outcomes among survivors, such as cognitive or functional status, were not available.

Conclusions

In adult patients with septic shock receiving norepinephrine, the use of vasopressin was variable. A reinforcement learning model developed and validated in several observational datasets recommended more frequent and earlier use of vasopressin than average care patterns and was associated with reduced mortality.

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ARTICLE INFORMATION

Accepted for Publication: February 27, 2025.

Published Online: March 18, 2025. doi:10.1001/jama.2025.3046

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Author Contributions: Dr Kalimouttou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Seymour and Pirracchio are co-senior authors.
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Conflict of Interest Disclosures: Dr Saria reported holding a leadership position at Bayesian Health; receiving honoraria for lectures on artificial intelligence and health from various tech, biotech, healthtech, and professional societies; and holding equity in several companies, including Bayesian Health, Century Health, Specta Health, Midstream Health, Latent Health, and Duality Tech.
Dr Seymour reported receiving grants from National Institutes of Health (NIH)/National Institute of General Medical Sciences; personal fees from Beckman Coulter, Octapharma, and Deepull outside the submitted work; and travel funding for research conferences from the International Sepsis Forum and the International Symposium on Intensive Care and Emergency Medicine.
Dr Pirracchio reported receiving grants from AOP Health during the conduct of the study; and research grants from NIH, Patient-Centered Outcomes Research Institute, and US Department of Defense. No other disclosures were reported.

Funding/Support: This article was funded in part by the NIH (Dr Seymour, R35GM119519) and by a research grant from AOP Health (Dr Pirracchio).

Role of the Funder/Sponsor: The NIH and AOP Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Dr Angus is a senior editor and Drs Seymour and Pirracchio are associate editors of *JAMA* but were not involved in any of the decisions regarding review of the manuscript or its acceptance.

Data Sharing Statement: See Supplement 2.

Additional Information: ChatGPT-4o (OpenAI) was used between September 2024 and February 2025 to check grammar and spelling. Dr Pirracchio takes responsibility for the integrity of the content generated.

REFERENCES

1. Fleischmann-Struzek C, Mellhammar L, Rose N, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med*. 2020;46(8):1552-1562. doi:10.1007/s00134-020-06151-x

2. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

3. Evans L, Rhodes A, Alhazzani W, et al. Executive summary: Surviving Sepsis Campaign: international guidelines for the management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):1974-1982. doi:10.1097/CCM.0000000000005357

4. Vail EA, Gershengorn HB, Hua M, Walkey AJ, Wunsch H. Epidemiology of vasopressin use for adults with septic shock. *Ann Am Thorac Soc*. 2016;13(10):1760-1767. doi:10.1513/AnnalsATS.201604-259OC

5. Sutton RS, Barto AG. The reinforcement learning problem. 1998. Accessed July 3, 2023. http://incompleteideas.net/book/first/Chap3PrePub.pdf

6. Collins GS, Moons KGM, Dhiman P, et al. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. *BMJ*. 2024;385:e078378. doi:10.1136/bmj-2023-078378

7. UCSF Data. How to get de-identified clinical data for cohort studies, pattern recognition, and more. Accessed January 12, 2024. https://data.ucsf.edu/research/deid-data

8. Johnson A, Bulgarelli L, Pollard T, Horng S, Celi LA, Mark R. MIMIC-IV. PhysioNet. March 16, 2021. Accessed March 3, 2025. https://physionet.org/content/mimiciv/1.0/

9. Pollard TJ, Johnson AEW, Raffa JD, Celi LA, Mark RG, Badawi O. The eICU Collaborative Research Database, a freely available multi-center database for critical care research. *Sci Data*. 2018;5:180178. doi:10.1038/sdata.2018.178

10. Seymour CW, Kennedy JN, Wang S, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA*. 2019;321(20):2003-2017. doi:10.1001/jama.2019.5791

11. Futoma J, Hughes M, Doshi-Velez F. POPCORN: Partially Observed Prediction Constrained Reinforcement Learning. March 31, 2020. Accessed March 3, 2025. https://finale.seas.harvard.edu/sites/g/files/omnuum4281/files/finale/files/popcorn_partially_observed_prediction_constrained_reinforcement_learning.pdf

12. Ernst D, Geurts P, Wehenkel L. Tree-based batch mode reinforcement learning. J Mach Learn Res. April 2005. Accessed March 3, 2025. https://www.jmlr.org/papers/volume6/ernst05a/ernst05a.pdf

13. Rubinstein RY, Kroese DP. *Simulation and the Monte Carlo Method*. John Wiley & Sons; 1981.

14. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22(7):707-710. doi:10.1007/BF01709751

15. Voloshin C, Le HM, Jiang N, Yue Y. Empirical study of off-policy policy evaluation for reinforcement learning. arXiv. Revised November 27, 2021. Accessed March 3, 2025. http://arxiv.org/abs/1911.06854

16. Precup D, Sutton RS, Singh S. Eligibility traces for off-policy policy evaluation. Accessed April 23, 2023. https://scholarworks.umass.edu/cgi/viewcontent.cgi?article=1079&context=cs_faculty_pubs

17. Tang S, Wiens J. Model selection for offline reinforcement learning: practical considerations for healthcare settings. *Proc Mach Learn Res*. 2021;149:2-35.

18. Peine A, Hallawa A, Bickenbach J, et al. Development and validation of a reinforcement learning algorithm to dynamically optimize mechanical ventilation in critical care. *NPJ Digit Med*. 2021;4(1):32. doi:10.1038/s41746-021-00388-6

19. Saria S. Individualized sepsis treatment using reinforcement learning. *Nat Med*. 2018;24(11):1641-1642. doi:10.1038/s41591-018-0253-x

20. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-3679. doi:10.1002/sim.6607

21. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167(4):268-274. doi:10.7326/M16-2607

22. Keele L, Zhao Q, Kelz RR, Small D. Falsification tests for instrumental variable designs with an application to tendency to operate. *Med Care*. 2019;57(2):167-171. doi:10.1097/MLR.0000000000001040

23. Psaty BM, Siscovick DS. Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction. *JAMA*. 2010;304(8):897-898. doi:10.1001/jama.2010.1205

24. Psaty BM, Koepsell TD, Lin D, et al. Assessment and control for confounding by indication in

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observational studies. *J Am Geriatr Soc*. 1999;47(6):749-754. doi:10.1111/j.1532-5415.1999.tb01603.x

25. Lundberg SM, Nair B, Vavilala MS, et al. Explainable machine-learning predictions for the prevention of hypoxaemia during surgery. *Nat Biomed Eng*. 2018;2(10):749-760. doi:10.1038/s41551-018-0304-0

26. Jafar A, Pasqua MR, Olson B, Haidar A. Advanced decision support system for individuals with diabetes on multiple daily injections therapy using reinforcement learning and nearest-neighbors: in-silico and clinical results. *Artif Intell Med*. 2024;148:102749. doi:10.1016/j.artmed.2023.102749

27. Lauffenburger JC, Yom-Tov E, Keller PA, et al. The impact of using reinforcement learning to personalize communication on medication adherence: findings from the REINFORCE trial. *Digit Med*. 2024;7(1):1-12. doi:10.1038/s41746-024-01028-5

28. Russell JA, Walley KR, Singer J, et al; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877-887. doi:10.1056/NEJMoa067373

29. Holmes CL, Patel BM, Russell JA, Walley KR. Physiology of vasopressin relevant to management of septic shock. *Chest*. 2001;120(3):989-1002. doi:10.1378/chest.120.3.989

30. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation*. 1997;95(5):1122-1125. doi:10.1161/01.CIR.95.5.1122

31. Sharshar T, Carlier R, Blanchard A, et al. Depletion of neurohypophyseal content of vasopressin in septic shock. *Crit Care Med*. 2002;30(3):497-500. doi:10.1097/00003246-200203000-00001

32. Sharshar T, Blanchard A, Paillard M, Raphael JC, Gajdos P, Annane D. Circulating vasopressin levels in septic shock. *Crit Care Med*. 2003;31(6):1752-1758. doi:10.1097/01.CCM.0000063046.82359.4A

33. Cowley AW Jr. Long-term control of arterial blood pressure. *Physiol Rev*. 1992;72(1):231-300. doi:10.1152/physrev.1992.72.1.231

34. Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. *Science*. 2019;366(6464):447-453. doi:10.1126/science.aax2342

35. Bitton E, Zimmerman S, Azevedo LCP, et al. An international survey of adherence to Surviving Sepsis Campaign guidelines 2016 regarding fluid resuscitation and vasopressors in the initial management of septic shock. *J Crit Care*. 2022;68:144-154. doi:10.1016/j.jcrc.2021.11.016

36. Zhang K, Wang H, Du J, et al. An interpretable RL framework for pre-deployment modeling in ICU hypotension management. *NPJ Digit Med*. 2022;5(1):173. doi:10.1038/s41746-022-00708-4

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